II. REMARKS

Upon entry of the amendment, claims 1 to 27 will be pending. For the Examiner's convenience, a marked-up copy of the claims showing the amendments is attached hereto as Exhibit A.

Applicant and Applicant's representative gratefully acknowledge the attention to the application and helpful suggestions made by the Examiner in a telephone conference held with Applicant's representative on June 20, 2001.

A. Regarding the Amendments

Claims 1 and 12 have been amended to delete reference to "lymph node" as a tissue to be examined, and new claims 20 and 25 have been added to encompass the subject matter deleted from claims 1 and 12. As such, the amendment to claims 1 and 12 does not add new matter, but merely separates the subject matter previously encompassed by claims 1 and 12 into separate independent claims.

Claims 2 and 11 have been amended to more clearly set forth the steps required to practice the invention. As such, the amendments merely address a formality, but do not add new matter.

New claims 19 to 27 have been added. New claim 19 is supported by previously pending claim 18, and, for example, page 9, lines 1-6. As such, new claim 19 does not add new matter.

New claims 20 and 25 are based on original claims 1 and 12, respectively, and, therefore, do not add new matter. New claims 21 to 24 are based on original claims 2 (including as amended herein), 4, 5, and 7and 8, respectively, and new claims 26 and 27 are based on original claims13 and 15. As such, newly added claims 20 to 27 do not add new matter.

B. Rejections under 35 U.S.C. §112

The rejection of claims 2, 3 and 11 under 35 U.S.C. §112, second paragraph, as allegedly indefinite is respectfully traversed.

It was stated in the Office Action mailed March 7, 2001, that the claims are indefinite in setting forth how, for example, the steps of claim 2 relate to claim 1. Based, in part, on the suggestions made by the Examiner in the telephone conference held June 20, 2001, claims 2 and 11 have been amended to more clearly define the steps required for practicing the claimed methods. Accordingly, it is respectfully requested that this rejection of the claims be removed.

C. Prior Art Rejections

The rejection of claims 1 to 6, 10 and 12 to 18 under 35 U.S.C. §103(a) as allegedly obvious over Sobol et al. in view of Effert et al. is respectfully traversed.

Sobol et al. is applied as describing methods for detecting carcinoma metastases by extracting nucleic acids from a sample and detecting a carcinoma associated sequence; as teaching a variety of targets other than a mutant target nucleic acid that may be analyzed; and as teaching that their methods are more sensitive than conventional methods, including histological analysis, that may fail to detect residual or metastatic disease. Effert et al. is applied as describing that p53 mutations are the most common single point mutations associated with cancer cells, and can be detected in primary tumors and in samples from sites of metastases, including lymph nodes.

It is maintained in the Office Action that it would have been *prima facie* obvious to modify the method of Sobol et al. to detect p53 mutations as described by Effert et al., for example, in histologically normal lymph node tissues from prostate cancer patients. The

motivation to combine the references is allegedly based on the reference by Effert et al. that mutations in metastatic sites may play a role in the progression of human prostate cancer, and the reference by Sobol et al. that their methods can detect metastases in tissues that appear normal histologically.

It is noted that amended claims 1 to 6, 10 and 12 to 17 are directed to examining a "tumor margin tissue sample." It is submitted that neither Sobol et al. nor Effert et al. teach or suggest examining a tissue sample obtained from tumor margin and, therefore, that the rejection is moot with respect to these claims (as well as to new claim 19). However, the rejection is addressed with respect to claim 18, which encompasses examining lymph node, and new claims 20 to 27, which are directed to examining lymph node.

Applicant maintains, however, that one of ordinary skill in the art would not have been motivated to combine the Sobol et al. reference, which describes that metastases that are not detectable by histological methods can be identified by detecting the expression of an otherwise normal gene product in cells in which it is not normally expressed, with the Effert et al. reference, which describes detecting mutant target nucleic acid sequences in tumor tissues, including in tumor metastases.

Applicant previously pointed out that Sobol et al. specifically state that "[i]n contrast to prior methods for cancer detection, the target nucleic acid is not necessarily an oncogene mRNA product." (column 4, lines 27-30). In response, the Examiner states that such language clearly indicates that the Sobol et al. method provides an improvement that may be used in detection of both oncogenic and non-oncogenic products (see Office Action, sentence bridging pages 6-7; emphasis in original).

While Applicant does not disagree that the statement "not necessarily an oncogene," when taken alone, can be interpreted to mean the target nucleic acid can be either an oncogenic or non-oncogenic product, it is submitted that the Sobol et al. reference, when viewed in its entirety, does not teach or suggest that the target nucleic acid can be an oncogenic product. Applicant submits that the statement by Sobol et al. at column 4, lines 27-29, is intended to distinguish the prior art. As such, the statement can be read as an indication that, in prior art methods (i.e., prior to that described by Sobol et al.), the target nucleic acid was "necessarily an oncogene." Thus, the statement by Sobol et al., at best, indicates that their method was distinguishable from previous methods, in which the target was "necessarily an oncogene."

In support of the above interpretation of the statement by Sobol et la., it is noted that the reference provides numerous examples of cellular gene products, which, when expressed in cells other than those normally expressing the gene product, can be indicative of a carcinoma (see column 5, lines 10-21, and column 11, line 3, to column 12, line 33). In addition, Sobol et al. disclose that expression of a virally encoded protein can be indicative of carcinoma cells (column 9, lines 46-51). Remarkably, however, the reference does not disclose any oncogenes, or a mutant target nucleic acid sequences, that can be examined according to a method of the invention as being indicative of a carcinoma. The absence of even a single example of an oncogene is particularly remarkable because such genes were well known in the art and the subject of intensive study before the earliest priority date of the Sobol et al. patent (see, for example, Effert et al., page 789, and references cited therein).

Since the Sobol et al. reference does not disclose a single example of an oncogene that can serve as a "carcinoma associated sequence," and since the reference only refers to an oncogene with respect to the prior art, it is submitted that the reference, when viewed in its entirety, does not support the position that the statement that "the target nucleic acid is not necessarily an oncogene mRNA product" clearly indicates that the method can be used in the

detection of both oncogenic and non-oncogenic products. Instead, it is submitted that the statement merely indicates that the prior art required that a target nucleic acid sequence was "necessarily an oncogene mRNA product." As such, Sobol et al. do not provide any suggestion that their method can be used to detect a mutant target nucleic acid sequence such as a mutant oncogene and, therefore, one of ordinary skill in the art, viewing the Sobol et al. reference, would not have been motivated to combine it with the Effert et al. reference, which describes detection of a mutant p53 oncogene.

Furthermore, Effert et al. do not provide any explicit disclosure that would have motivated one in the art to combine it with the Sobol et al. reference. Effert et al. only examine tumor tissues (see, for example, page 790, right column, first full paragraph; page 791, paragraph bridging columns, and right column, first full paragraph). Effert et al. suggest that mutation of p53 in a primary tumor and loss of heterozygosity of 17p may contribute to the progression of human prostate cancer (page 789, right column, second full paragraph), and state that these markers can be useful for grading and staging prostate adenocarcinoma (paragraph bridging pages 792-793). However, the reference solely addresses detecting mutations in cells that were histologically confirmed to be cancer cells (see, for example, page 791, paragraph bridging columns), but does not teach or suggest that the detection of such mutations can be useful for identifying a cancer in a region that otherwise appears normal.

In summary, Sobol et al. describe a method of detecting a carcinoma by detecting the expression of a carcinoma associated mRNA in a cell other than that in which it is normally expressed, but does not teach or suggest that the carcinoma associated mRNA can be an oncogene product or a mutant target nucleic acid sequence. In comparison, Effert et al. describe that p53 mutations and loss of heterozygosity of 17p in tumor can be indicative of the progression of a cancer, but do not teach or suggest that such mutations can be indicative of a cancer in cells that appear histologically normal. Thus, absent Applicant's disclosure, it is

submitted that one of ordinary skill in the art would not have been motivated to use the method of Sobol et al. to detect a mutant nucleic acid as suggested by Effert et al. because Sobol et al. specifically disclose the detection of otherwise normal gene products and because Effert et al. only describe examining tumor tissues. Accordingly, it is submitted that the claimed invention would not have been obvious over Sobol et al. in view of Effert et al. and, therefore, respectfully requested that the previous rejection of the claims under 35 U.S.C. §103(a) be removed and that the rejection not be made with respect to the newly added claims.

The rejection of claims 7 to 9 under 35 U.S.C. §103(a) as allegedly obvious over Sobol et al. in view of Effert et al., and further in view of McAnalley et al. is respectfully traversed.

It is noted that amended claims 7 to 10 are directed to examining a "tumor margin tissue sample." It is submitted that the cited reference, either alone or in combination, teach or suggest examining a tissue sample obtained from tumor margin and, therefore, that the rejection is moot with respect to these claims. However, the rejection is addressed with respect to new claims 20 and 24, which are directed to examining lymph node and encompass the subject matter at issue.

Sobol et al. and Effert et al. are applied as discussed above. McAnalley et al. is applied as describing a variety of tumor types, including benign neoplasms and malignant neoplasms of the head and neck. It is maintained that, in view of such teachings, it would have been *prima facie* obvious to modify the method of Sobol et al. in view of Effert et al. to detect nucleic acid targets associated with such neoplasms. However, for the reasons discussed above, it is submitted that one skilled in the art would not have been motivated to combine the Sobol et al. and Effert et al. reference. McAnalley et al. do not cure this defect and, therefore, it is submitted that the claimed invention would not have been obvious over Sobol et al. in view of Effert et al., and further in view of McAnalley et al. Accordingly, it is respectfully requested that the

previous rejection of the claims under 35 U.S.C. §103(a) be removed and that the rejection not be made with respect to the newly added claims.

The rejection of claim 11 under 35 U.S.C. §103(a) as allegedly obvious over Sobol et al. in view of Effert et al., and further in view of Mullis et al. (U.S. Pat. No. 4,683,195) is respectfully traversed.

It is noted that amended claim 11 is directed to examining a "tumor margin tissue sample." It is submitted that the cited reference, either alone or in combination, teach or suggest examining a tissue sample obtained from tumor margin and, therefore, that the rejection is moot with respect to these claims. However, the rejection is addressed with respect to new claims 20, which is directed to examining lymph node and encompasses the subject matter at issue.

Sobol et al. and Effert et al. are applied as discussed above. Mullis et al. is applied as teaching such cloning of an amplification product. It is maintained that, in view of such teachings, it would have been *prima facie* obvious to modify the method of Sobol et al. in view of Effert et al. to detect nucleic acid targets associated with such neoplasms. However, for the reasons discussed above, it is submitted that one skilled in the art would not have been motivated to combine the Sobol et al. and Effert et al. reference. Mullis et al. do not cure this defect and, therefore, it is submitted that the claimed invention would not have been obvious over Sobol et al. in view of Effert et al., and further in view of Mullis et al. Accordingly, it is respectfully requested that the previous rejection of the claims under 35 U.S.C. §103(a) be removed and that the rejection not be made with respect to the newly added claims.

D. Double Patenting Rejection

The rejection of the claims under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1 to 4 of U.S. Pat. No. 6,025,127 is respectfully traversed. Although the rejection is traversed, Applicant respectfully defers responding to the rejection until an indication is received that one or more claims are in condition for allowance.

III. CONCLUSION

In view of the amendments and the above remarks, it is submitted that the claims are in condition for allowance and a notice to that effect is respectfully requested. The Examiner is invited to contact the undersigned if there are any questions relating to the subject application.

Please charge any additional fees, or make any credits, to Deposit Account No. 50-1355.

Respectfully submitted,

Date: August 6, 2001

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Enclosure: Exhibit A

In re Application of
David Sidransky
U.S. Serial No.: 09/420,433
Filed: October 12, 1999
Exhibit A .

PATENT
Attorney Docket No.: JHU1180-1

EXHIBIT A

MARKED-UP COPY OF THE CLAIMS SHOWING THE AMENDMENTS

1. (Twice amended) A method for detecting the presence of a mammalian mutant target nucleic acid which contributes to the etiology of a neoplasm, in a tumor margin tissue specimen, wherein the specimen is external to a primary neoplasm and the specimen does not exhibit morphological characteristics indicative of neoplastic pathology, and the mutant target nucleic acid is present in the primary neoplasm and the specimen, [the specimen being selected from the group consisting of a tumor margin and a regional lymph node,] the method comprising extracting nucleic acid present in the specimen and detecting the presence of the mutant target nucleic acid.

2. (Twice amended) The method of claim 1, further comprising, prior to detecting the presence of the mutant nucleic acid, amplifying the nucleic acid present in the specimen to produce an amplified nucleic acid, wherein said detecting comprises [before] detecting the presence of the mutant target nucleic acid in the amplified nucleic acid.

11. (Twice amended) The method of claim 2, further comprising, prior to detecting the presence of the mutant nucleic acid, cloning the amplified nucleic acid, wherein said detecting comprises [before] detecting the presence of the mutant target nucleic acid in the amplified nucleic acid.

12. (Twice amended) A method for detecting metastases in a subject having an excised tumor, the method comprising:

a) isolating tissue from a surgical margin [or lymph node] adjacent to the excised tumor;

b) applying to said tissue an oligonucleotide that specifically hybridizes to a neoplastic nucleic acid having a mutant nucleotide sequence; and

c) detecting the presence of said neoplastic nucleic acid, wherein the presence of said neoplastic nucleic acid indicates metastases.